UNIVERSITY OF KWAZULU-NATAL ™

INYUVESI YAKWAZULU-NATALI

HIV DRUG RESISTANCE
WHAT'S THE CURRENT SITUATION?

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Definitions

Acquired drug resistance (ADR)

Drug resistance in a person who has taken ART – results from genetic variation in the population of viruses and selection of resistant variants during treatment

Transmitted drug resistance (TDR)

Drug resistance in a person previously untreated with ART – that person has been infected by virus with drug resistance mutations

Pre-treatment drug resistance (PDR)

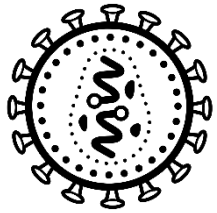
Drug resistance in a person initiating or re-initiating ART (i.e. with or without prior ARV exposure). PDR can be a mix of TDR & ADR

Consequences of HIVDR

In a situation with PDR >10%, HIVDR is projected to account for the following in Africa by 2030:

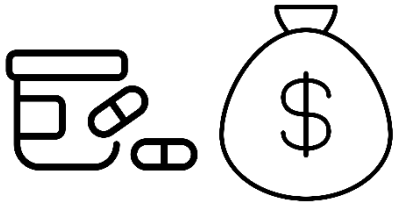
890 000 deaths

~1 in 6
HIV-related deaths



450 000 new infections

~1 in 10
new infections

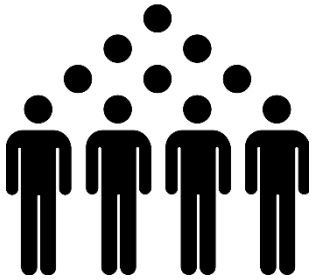


$6.5 billion ART programme costs

~$1 for every $12 cost

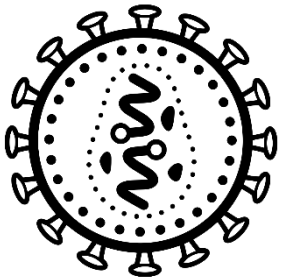
Source: Phillips et al. JID 2017

Acquired drug resistance



Increasing numbers of people on ART
>3.6 million on ART (>1.3 million in KZN)

Persistent challenges, gaps, weaknesses
For patients and health system



Acquired drug resistance
Inevitable consequence

Acquired drug resistance
National survey 2013-2014

- Cross-sectional survey (91 facilities)
- Adults (≥18yrs) on NNRTI-based ART with 2 x VL>1000
- N = 788
- Median time on ART 36 months (IQR 19–59)
- 82% EFV; 74% TDF + FTC/3TC
- >40% exposed to d4T or AZT

Source: Steegen JAC 2016

What proportion had evidence of acquired drug resistance (i.e. at least one drug resistance mutation)?

A. <10%

B. 50%

C. 70%

D. 85%

E. >95%

Acquired drug resistance
National survey 2013-2014

96% at least one drug resistance mutation (DRM)

>90% both NNRTI & NRTI mutations

M184V – 83%

K65R – 46%

≥1 TAM – 27%

TAM – thymidine analogue mutation

Source: Steegen JAC 2016

Acquired drug resistance
KZN study 2013

- Cross-sectional survey (15 facilities KZN)
- Adults (≥18yrs) on first-line ART for 12-15 months (group A) or 24-36 months (group B)
- VL measurement - virological failure definition: VL >1000 copies/mL
- Genotypic resistance testing if VL >1000 copies/mL
- N = 1299 (540 group A, 759 group B)

Source: Hunt JAC 2017

What proportion of those in group B (24-36 months on first-line ART) had evidence of acquired drug resistance (i.e. at least one drug resistance mutation)?

A. <10%

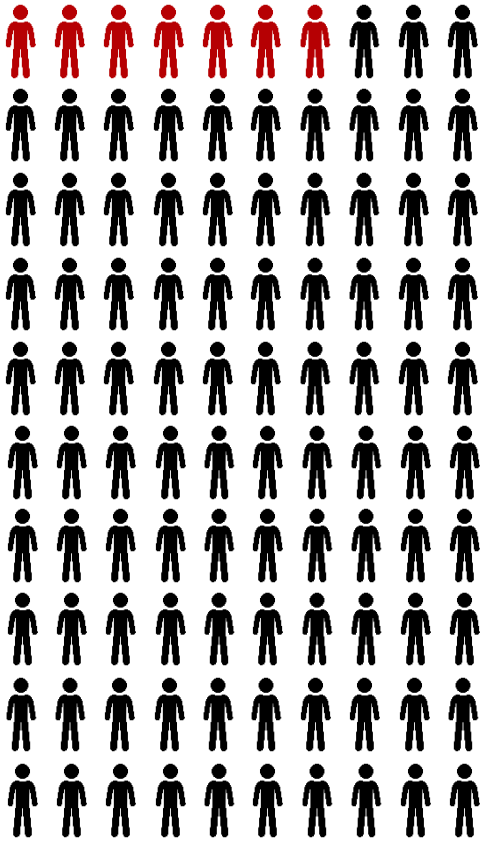
B. 15%

C. 25%

D. 35%

E. >50%

Acquired drug resistance
KZN survey 2013



~7% overall (in group B) had evidence of ADR

Group	% VL>1000	% DRM	% ADR
A	4.0%	84.2%	3.4%
B	7.7%	89.4%	6.9%

So although most people with virological failure had ADR, most people did not have virological failure

Source: Hunt JAC 2017

Acquired drug resistance
Delays in switch to second-line ART

- SA multicentre study (9 sites) following adults on first-line ART with virological failure[1]
  - 37% did not switch to second-line ART
  - In those that did switch, median time to switch 3.4 months
- Much longer delays reported from sites in KZN
  - Median delay 13 months eThekwini[2]
  - Median delay 27 months Hlabisa[3]
- Increasing evidence that delays increase risk of OI and death[4]

Sources: 1. Rohr PLoS One 2016; 2. Narainsamy SAJHIVMed 2017; 3. Manasa PLoS One 2013; 4. Murphy ARHR 2017

Acquired drug resistance: second-line ART
National survey 2013-14

- Cross-sectional survey (72 facilities)
- Adults (≥18yrs) on PI-based ART regimen with single VL>1000
- N = 350
- Median time on PI regimen 25months (IQR 14-43)
- Median total time on ART 62 months (IQR 46-85)
- >90% LPV/r (around half on TDF, half on AZT)

Source: Steegen JID 2016

Approximately what proportion had at least one major protease mutation?

A. <10%

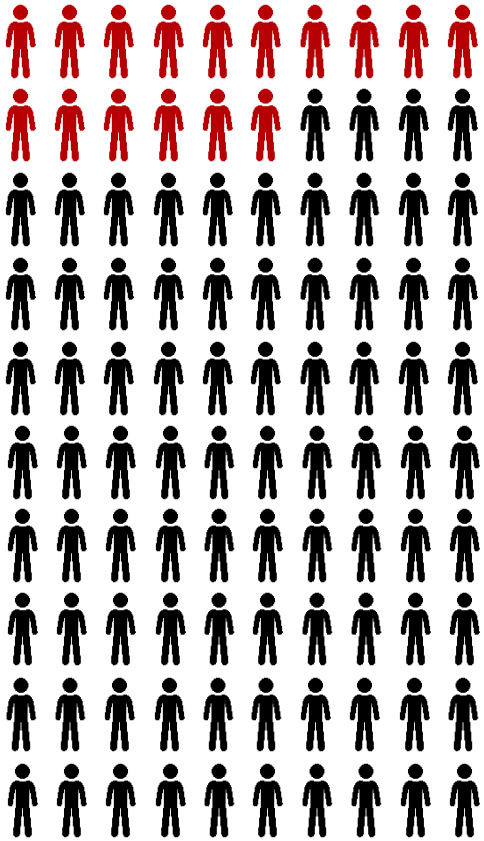
B. 15%

C. 25%

D. 50%

E. >75%

Acquired drug resistance: second-line ART
National survey 2013-2014



16% at least one major protease mutation

60% had ≥1 NRTI mutation

65% had residual NNRTI mutations

25% had no drug resistance mutations at all

Source: Steegen JID 2016

Is there any evidence that increasing ADR is leading to an increase in transmitted drug resistance?

A. Yes

B. No

C. I have no idea, that's what you're here to tell me

Pre-treatment drug resistance
National survey 2013-2014

- Cross-sectional survey
- Adults (≥18yrs) initiating ART or attending pre-ART follow-up visit
- Without prior ART exposure (based on self-report, excluding pMTCT)
- N = 277
- 59% female; median age 34 yrs
- Median CD4+ count 149 cells/μL

Source: Steegen PLoS One 2016

What proportion had PDR (any mutation)?

A. <5%

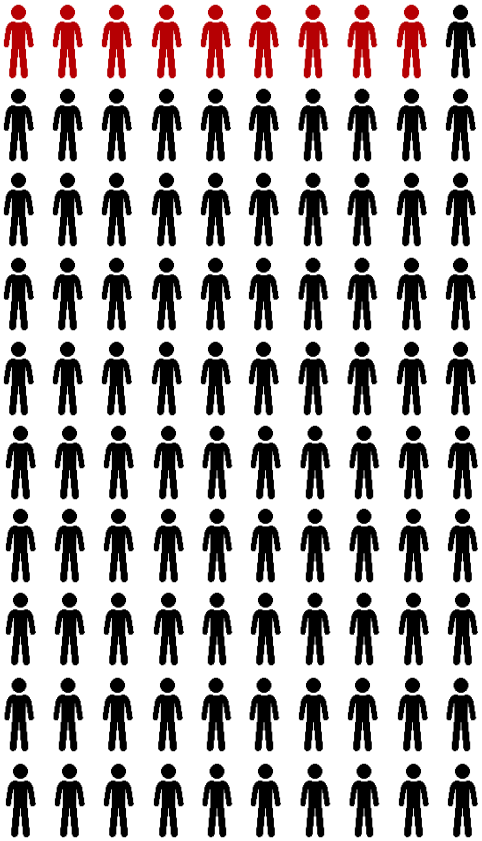
B. 5-10%

C. 10-15%

D. 15-20%

E. >20%

Pre-treatment drug resistance
National survey 2013-2014



9% (25/277) had at least one drug resistance mutation (DRM)

NNRTI – 8.3%
NRTI – 2.5%
PI – 0.7%

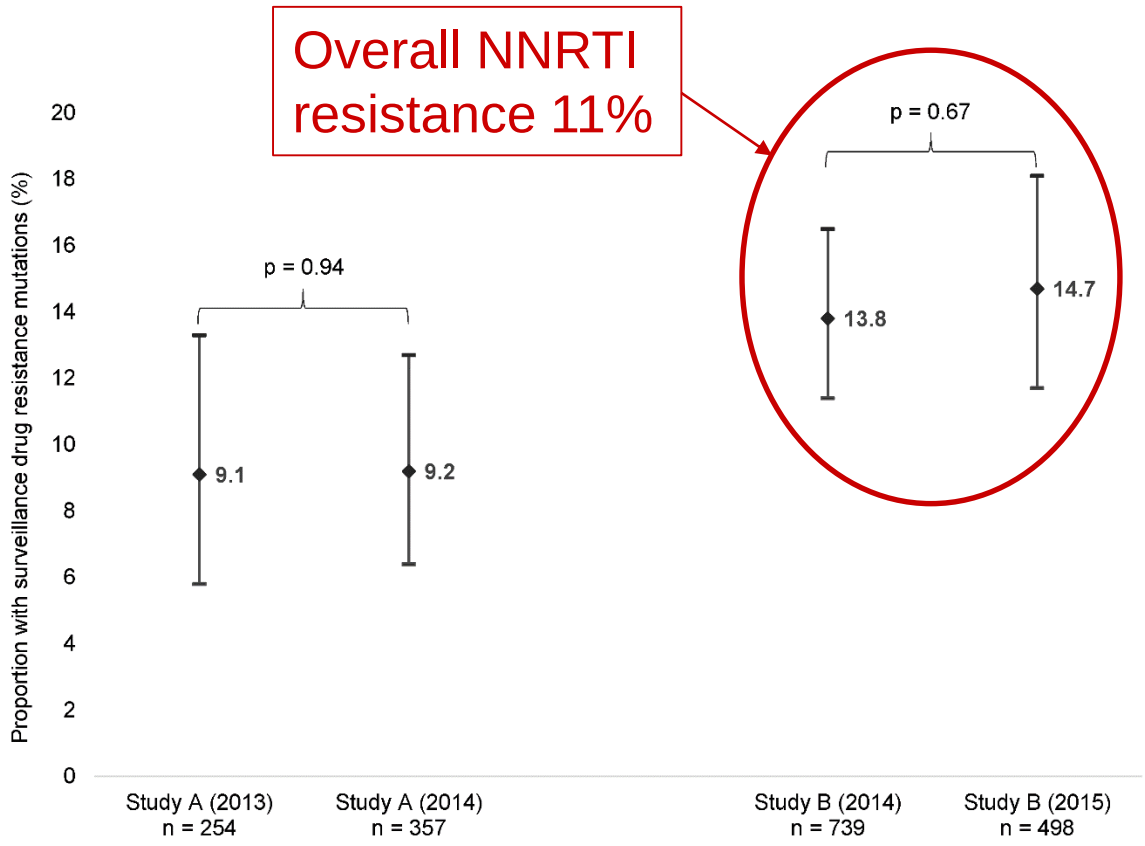
Most common mutations - K103N (5.8%), Y181C (2.2%), K65R (1.4%)

Source: Steegen PLoS One 2016

Pre-treatment drug resistance
KZN data 2013-15

Two rural population-based HIV surveillance studies

HIV-positive individuals with no documented exposure to ART

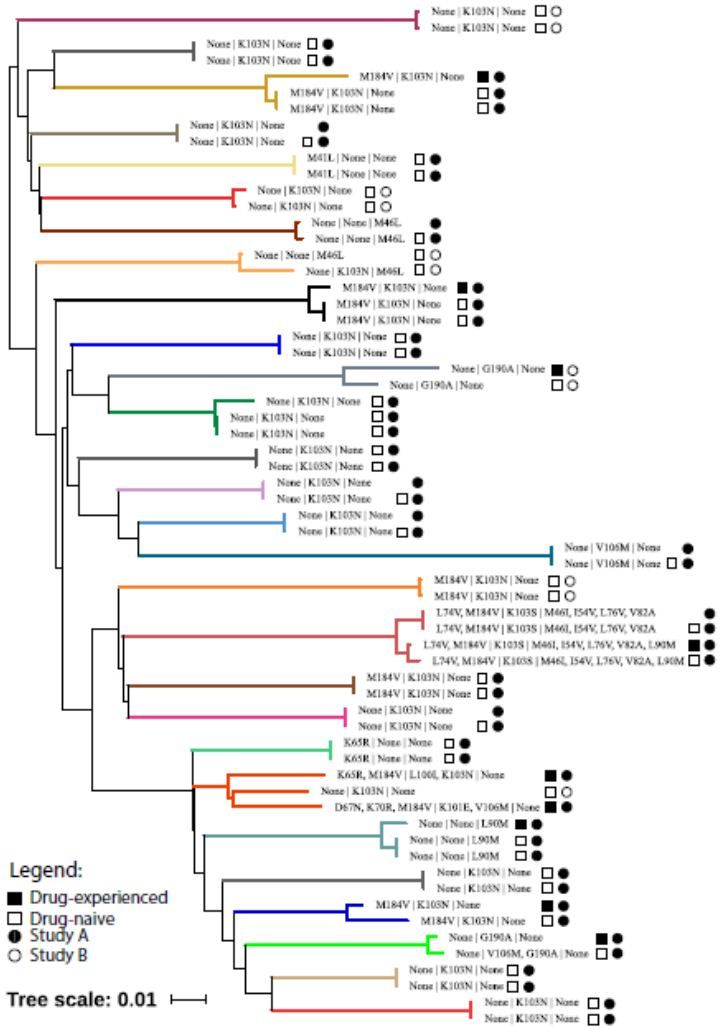


Unpublished data: Chimukangara et al.

Pre-treatment drug resistance
KZN data 2013-15

Phylogenetic analysis did not uncover any large transmission chains of drug-resistant virus

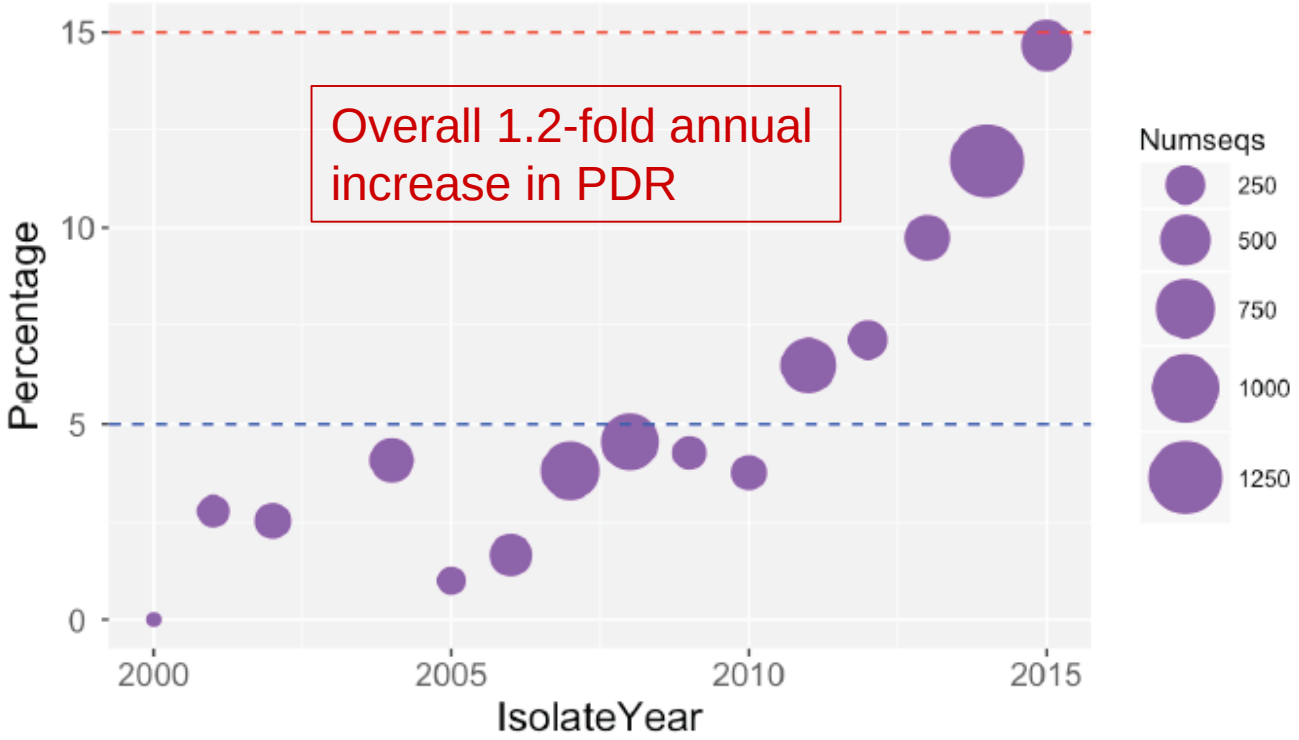
More likely several independent transmission events from people with ADR on ART



Unpublished data: Chimukangara et al.

Pre-treatment drug resistance
Trends in South Africa

Trends in PDR from all published & unpublished South African studies (21 studies, 5861 HIV-1 sequences)



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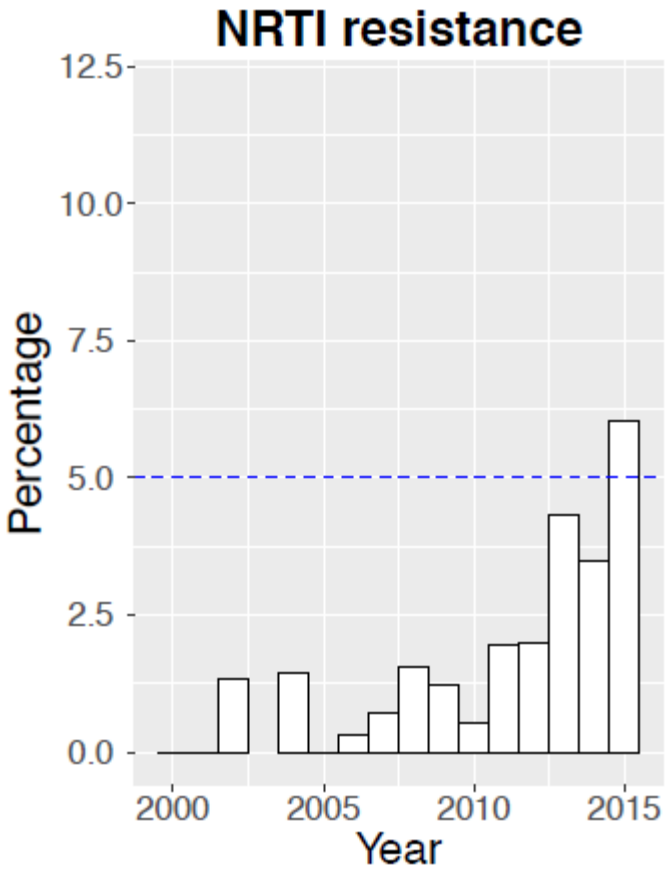
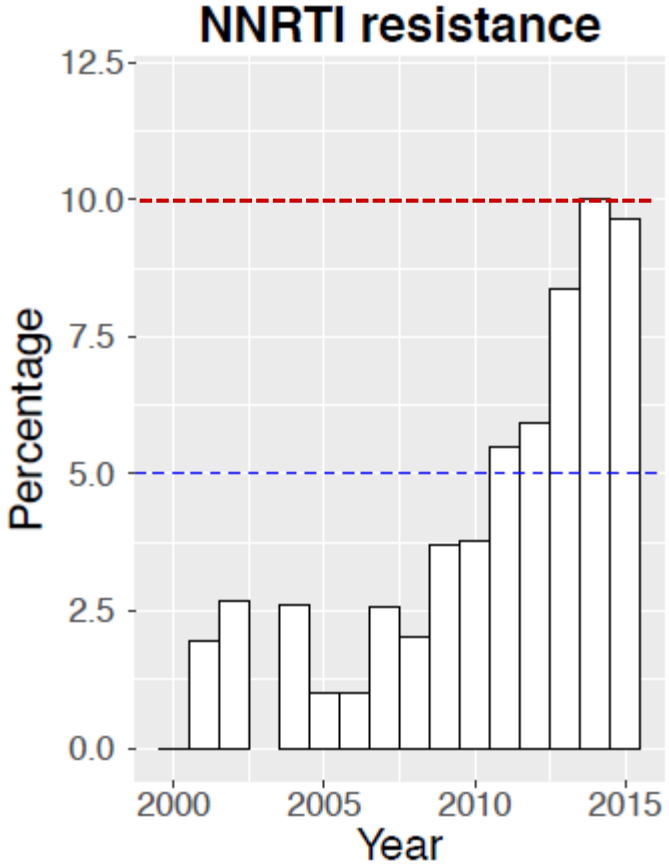
Pre-treatment drug resistance
Trends in South Africa





Unpublished data: Chimukangara et al.

What should we do in light of these levels of PDR?

A. Stop roll-out of ART immediately

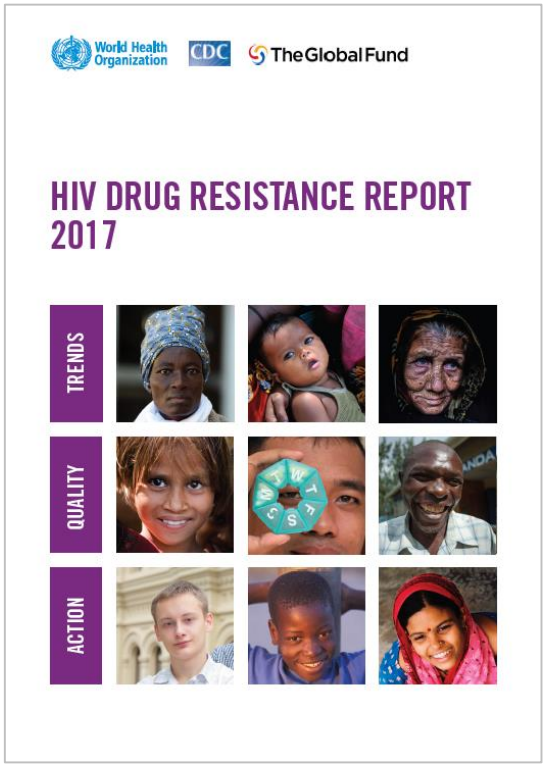
B. Introduce resistance testing for all pe
initiating ART

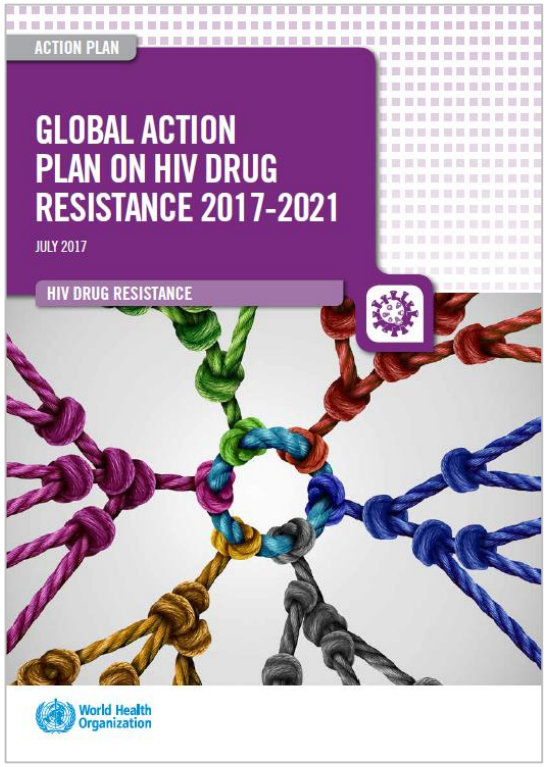
C. Introduce VL testing at 3 months and it ch ART
for those with early virological failur

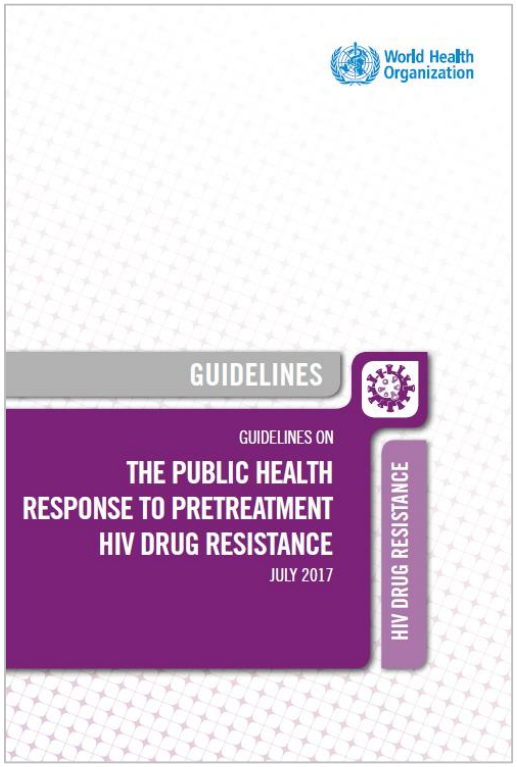
D. Change the standard first-line ART e n

E. Nothing at all

WHO guidance







"Countries in which the prevalence of PDR to NNRTIs is ≥10% should urgently consider an alternative first-line regimen that does not contain NNRTIs (preferred alternative TDF+3TC/FTC+DTG)"

Key messages

- Inevitable increase in number of people in the population with acquired HIV drug resistance
- Evidence suggests that TDR/PDR is increasing steadily - findings from KZN suggest we may already have crossed threshold for urgent action
- Change in first-line ART regimen is imminent
- Big mistake to think this alone is the answer: needs additional public health measures - focus on quality of prevention, treatment and care

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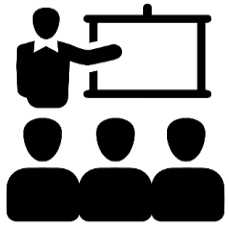
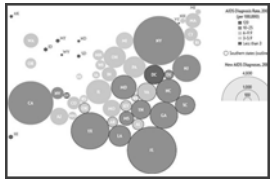
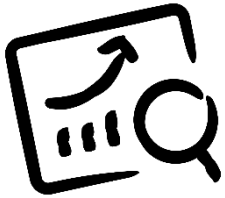


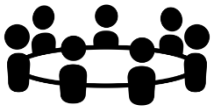
Training & capacity building – workshops, case book



Surveillance and real-time data visualization



Research – epidemiology, clinical & operational research



Stakeholder engagement – DoH, NHLS, partners